

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for the treatment of rheumatoid arthritis, comprising administering a compound of formula I



wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n ,

wherein n is 0-3 and each X is independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^5$, $-\text{C}(\text{O})\text{NR}^5\text{R}^5'$, $-\text{C}(\text{O})\text{R}^5$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{SR}^5$, $-\text{NR}^5\text{R}^5'$, $-\text{NR}^5\text{C}(\text{O})\text{OR}^5'$, $-\text{NR}^5\text{C}(\text{O})\text{R}^5'$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_3\text{-C}_{13}$ heteroaryl, $\text{C}_4\text{-C}_{23}$ alk heteroaryl, substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_2\text{-C}_{10}$ alkenyl, substituted $\text{C}_1\text{-C}_{10}$ alkoxy, substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted $\text{C}_4\text{-C}_{23}$ alk heteroaryl and $-\text{Y}-\text{Ar}$;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^5$, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{O})\text{NR}^5\text{R}^5'$, $-\text{OR}^5$, $-\text{SR}^5$, $-\text{NR}^5\text{R}^5'$, $-\text{NO}_2$, $-\text{NR}^5\text{C}(\text{O})\text{R}^5'$, $-\text{NR}^5\text{C}(\text{O})\text{OR}^5'$ and halogen up to per-halosubstitution;

wherein R^5 and R^5' are independently selected from H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_3\text{-C}_{13}$ heteroaryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_4\text{-C}_{23}$ alk heteroaryl, up to per-halosubstituted $\text{C}_1\text{-C}_{10}$ alkyl, up to per-halosubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, up to per-halosubstituted $\text{C}_2\text{-C}_{10}$ alkenyl, up to per-halosubstituted $\text{C}_6\text{-C}_{14}$ aryl and up to per-halosubstituted $\text{C}_3\text{-C}_{13}$ heteroaryl,

wherein Y is $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^5)-$, $-(\text{CH}_2)_m-$, $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_m\text{O}-$, $-(\text{CH}_2)_m\text{S}-$, $-(\text{CH}_2)_m\text{N}(\text{R}^5)-$, $-\text{O}(\text{CH}_2)_m-$, $-\text{CHX}^a$, $-\text{NR}^5\text{C}(\text{O})\text{NR}^5\text{R}^5'$, $-\text{NR}^5\text{C}(\text{O})-$,

-C(O)NR⁵-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁵)(CH₂)_m-,

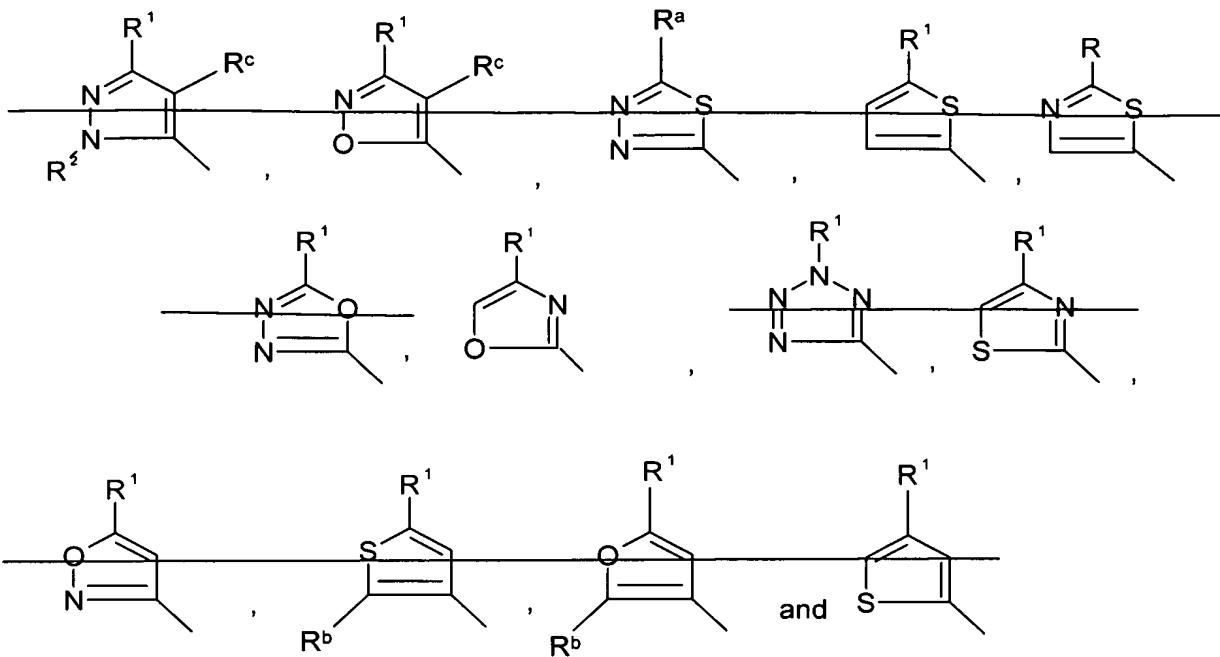
m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to perhalosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R⁵, -C(O)-NR⁵, -NO₂, =O, -OR⁵, -SR⁵, -NR⁵R⁵, -C(O)R⁵, -SO₂R⁵, -SO₂NR⁵R⁵, -NR⁵C(O)OR⁵, -NR⁵C(O)R⁵, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₃-C₁₀ cycloalkyl, substituted C₇-C₂₄ alkaryl and substituted C₄-C₂₃ alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)R⁵, -C(O)NR⁵R⁵, =O, -OR⁵, -SR⁵, -NO₂, -NR⁵R⁵, -NR⁵C(O)R⁵, -NR⁵C(O)OR⁵, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C-C₁₀ heteroaryl, C₆-C₁₄ aryl, C₄-C₂₄ alkheteroaryl and C₇-C₂₄ alkaryl

A is a heteroaryl moiety selected from the group consisting of



wherein

R^1 is selected from the group consisting of halogen, C_3 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_1 - C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1 - C_{10} alkyl, up to per-halosubstituted C_3 - C_{10} cycloalkyl, up to per-halosubstituted C_1 - C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl;

R^2 is selected from the group consisting of H , $C(O)R^4$, CO_2R^4 , $C(O)NR^3R^{3'}$, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_7 - C_{24} alkaryl, C_4 - C_{23} alkheteroaryl, substituted C_1 - C_{10} alkyl, substituted C_3 - C_{10} cycloalkyl, substituted C_7 - C_{24} alkaryl and substituted C_4 - C_{23} alkheteroaryl,

where R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of CN , CO_2R^4 , $C(O)NR^3R^{3'}$, $-NO_2$, OR^4 , SR^4 , and halogen up to per-halosubstitution;

wherein R^3 and $R^{3'}$ are independently selected from the group consisting of H , OR^4 , SR^4 , NR^4R^4 , $C(O)R^4$, CO_2R^4 , $C(O)NR^4R^4$, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, C_3 - C_{13} heteroaryl, C_7 - C_{24} alkaryl, C_4 - C_{23} alkheteroaryl, up to per-halosubstituted C_1 - C_{10} alkyl, up to per-halosubstituted C_3 - C_{10} cycloalkyl, up to per-halosubstituted C_6 - C_{14} aryl and up to per-halosubstituted C_3 - C_{13} heteroaryl; and

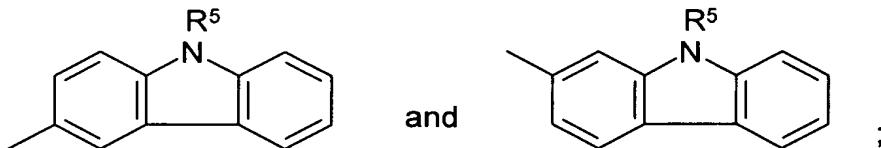
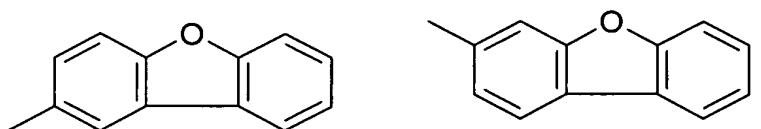
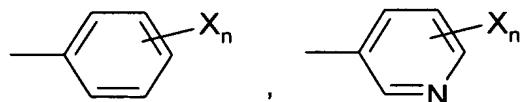
wherein R^4 and $R^{4'}$ are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

R^6 is C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₁-C₁₀ alkyl and up to per-halosubstituted C₃-C₁₀ cycloalkyl; and

R^b is hydrogen or halogen,

R^e is hydrogen, halogen, C₁-C₁₀ alkyl, up to per-halosubstituted C₁-C₁₀ alkyl or combines with R^4 and the ring carbon atoms to which R^4 and R^e are bound to form a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected from O, N and S.

2. (Original) A method as in claim 1, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of



which is substituted or unsubstituted by halogen, up to per-halosubstitution, and

wherein n = 0-3 and each X is independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R^{5'}, -C(O)R⁵, -NO₂, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NR⁵C(O)OR⁵, -NR⁵C(O)R^{5'}, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C₆-C₁₄

aryl, C₇-C₂₄ alkaryl, C₃-C₁₃ heteroaryl, C₄-C₂₃ alkheteroaryl, and substituted C₁-C₁₀ alkyl, substituted C₂-C₁₀-alkenyl, substituted C₁-C₁₀-alkoxy, substituted C₃-C₁₀ cycloalkyl, substituted C₄-C₂₃ alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)R⁵, -C(O)NR⁵R^{5'}, -OR⁵, -SR⁵, -NR⁵R^{5'}, NO₂, -NR⁵C(O)R^{5'}, -NR⁵C(O)OR^{5'} and halogen up to per-halosubstitution;

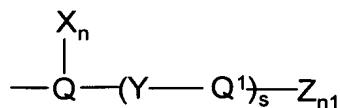
wherein R⁵ and R^{5'} are independently selected from H, C₁-C₁₀ alkyl, C₂-C₁₀-alkenyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₂-C₁₀-alkenyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

wherein Y is -O-, -S-, -N(R⁵)-, -(CH₂)_m, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -NR⁵C(O)NR⁵R^{5'}-, -NR⁵C(O)-, -C(O)NR⁵-, -(CH₂)_mS-, -(CH₂)_mN(R⁵)-, -O(CH₂)_m-, -CHX^a, -CX^a₂-, -S-(CH₂)_m- and -N(R⁵)(CH₂)_m-,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{nl}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)R⁵, =O, -SO₂R⁵, -SO₂NR⁵R^{5'}, -C(O)NR⁵R^{5'}, -C(O)R⁵, -NO₂, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NR⁵C(O)OR^{5'}, -NR⁵C(O)R^{5'}, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₃-C₁₀ cycloalkyl, substituted C₇-C₂₄ alkaryl and substituted C₄-C₂₃ alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R^{5'}, =O, -OR⁵, -SR⁵, -NO₂, -NR⁵R^{5'}, -NR⁵C(O)R^{5'}, -NR⁵C(O)OR^{5'}, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C₇-C₂₄ heteroaryl, C₆-C₁₄ aryl, C₄-C₂₃ alkheteroaryl and C₇-C₂₄ alkaryl.

3. (Previously Presented) A method of claim 1, wherein B is



wherein Y is selected from the group consisting of -O-, -S-, -CH₂-, -SCH₂-, -CH₂S-, -CH(OH)-, -C(O)-, -CX^a₂, -CX^aH-, -CH₂O- and -OCH₂-, where X^a is halogen, Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q¹ is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution, and

X, Z, n and n1 are as defined in claim 1 and s is 0 or 1.

4. (Original) A method as in claim 3, wherein

Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,

Q¹ is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or -Y-Q¹ is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and

Z and X are independently selected from the group consisting of -R⁶, -OR⁶ and -NHR⁷, wherein R⁶ is hydrogen, C₁-C₁₀-alkyl or C₃-C₁₀-cycloalkyl and R⁷ is selected from the group consisting of hydrogen, C₃-C₁₀-alkyl, C₃-C₆-cycloalkyl and C₆-C₁₀-aryl, wherein R⁶ and R⁷ can be substituted by halogen or up to per-halosubstitution.

5. (cancelled)

6. (cancelled)

7. (cancelled)

8. (currently amended) A method as in claim 15, wherein R¹ is t-butyl.

9. (cancelled)

10. (cancelled)

11. (cancelled)

12. (cancelled)

13. (cancelled)

14. (cancelled)

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22. (cancelled)

23. (cancelled)

24. (cancelled)

25. (cancelled)

26. (cancelled)

27. (cancelled)

28. (original) A method as in claim 1, wherein the compound for formula I displays p38 IC₅₀'s of less than 10 µm as determined by an in-vitro p38 kinase inhibition assay.

29. (cancelled)

30. (Original) A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

31. (cancelled)

32. (cancelled)

33. (cancelled)

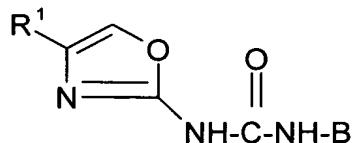
34. (cancelled)

35. (cancelled)

36. (cancelled)

37. (cancelled)

38. (Currently amended) A method as in claim 1 comprising administering a compound of the formula



wherein R¹ is t-butyl and B are as defined in claim 1.

39. (cancelled)

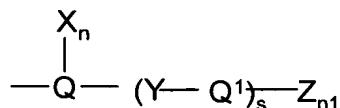
40. (cancelled)

41. (cancelled)

42. (cancelled)

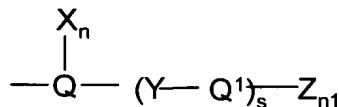
43. (cancelled)

44. (Currently amended) A method as in claim 1 5, wherein B is of the formula



wherein Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q¹ is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is -O-, -S-, -CH₂S-, -SCH₂-, -CH₂O-, -OCH₂- or -CH₂-, X is C₁-C₄ alkyl or up to per-halosubstituted C₁-C₄ alkyl and Z is as defined in claim 1, n = 0 or 1, s = 1 and n1 = 0-1.

45. (currently amended) A method as in claim 38 9, wherein B is of the formula



Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q¹ is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is -O-, -S-, -C(O)- or -CH₂-, X is C₁-C₄ alkyl or up to per-halosubstituted C₁-C₄ alkyl and Z is as defined in claim 1 n = 0 or 1, s = 0 or 1 and n1 = 0 or 1.

46. (cancelled)

47. (cancelled)

48. (cancelled)

49. (cancelled)

50. (Previously Presented) A method as in claim 1, wherein B is

a) phenyl, pyridinyl, naphthyl, quinoliny1 or isoquinoliny1, substituted by -Y-Ar and optionally substituted by

- halogen up to per-halosubstitution,
- C₁-C₄ alkyl,
- up to per-halosubstituted C₁-C₄ alkyl, or
- a combination thereof,

wherein Y and Ar are as defined in claim 1;

- b) thienyl substituted by methyl; or
- c) indolyl substituted by phenyl or pyridyl.

51. (Previously Presented) A method as in claim 1, wherein B is phenyl or pyridinyl substituted by -Y-Ar and optionally substituted by

- halogen ,up to per-halosubstitution,
- C₁-C₄ alkyl,
- up to per-halosubstituted C₁-C₄ alkyl, or

- a combination thereof,

wherein Y and Ar are as defined in claim 1.

52. (cancelled)

53. (Withdrawn currently amended) A pharmaceutical composition comprising a compound according to claim 52 1 or a pharmaceutically acceptable salt thereof and a physiologically acceptable carrier.

54. (cancelled)

55. (Previously Presented) A method according to claim 1, wherein R¹ is selected from the group consisting of halogen, C₃-C₁₀ cycloalkyl, C₁-C₁₃ heteroaryl, C₆₋₁₄ aryl, C₇₋₂₄ alkaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₁-C₁₃ heteroaryl, up to per-halosubstituted C₆₋₁₄ aryl, and up to per-halosubstituted C₇₋₂₄ alkaryl.

56. (cancelled)

57. (cancelled)

58. (Previously Presented) A method for the treatment of rheumatoid arthritis comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of formula

